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Iron deficiency anaemia in chronic inflammatory rheumatic diseases: low mean cell haemoglobin is a better marker than low mean cell volume

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Iron deficiency anaemia (IDA) is a common and complex problem in chronic inflammatory rheumatic diseases. The predominant cause of IDA is gastrointestinal blood loss, often due to drug treatment. However, asymptomatic colonic and gastric carcinoma may present with IDA and exclusion of these conditions is of prime concern.

The British Society of Gastroenterology has recently revised the guidelines for the diagnosis and management of IDA in the general population.[1] These guidelines use a combination of low haemoglobin, low mean cell volume (MCV), and low serum ferritin to diagnose IDA.

Diagnosing IDA in the presence of chronic inflammation as seen in rheumatoid arthritis, poses considerable difficulty because serum ferritin is an acute phase reactant and rises in the presence of inflammation. A further complicating factor in our population is that MCV tends to be spuriously raised as a result of disease modifying antirheumatic drug (DMARD) treatment—in particular, sulfasalazine, methotrexate, and azathioprine.

It has been suggested by Jolobe[2] and Broin *et al*[3] that low mean cell haemoglobin (MCH) correlates better with low ferritin levels and hence is better than low MCV as an aid to identifying patients with IDA, though this is still not widely used in routine clinical practice.

This study aimed at investigating whether MCV or MCH in combination with serum ferritin could be used effectively in screening for IDA in our patients.

METHODS AND RESULTS

We undertook a retrospective study of our patients with chronic inflammatory rheumatic diseases who were receiving regular blood monitoring for second line treatment. Those who were anaemic (haemoglobin <115 g/l in women and <130 g/l in men, which are the lower limits of normal range of haemoglobin concentration for the local laboratory[1]) on at least two occasions at least 1 month apart, were identified from ''drug monitoring records''. Further, those who were ''iron deficient'' were identified from APEX (computerised laboratory results system) based on low serum ferritin (<20 μg/l), low MCV (<80 fl), and low MCH (<27 pg).

A total of 1231 records were examined (patient characteristics are outlined in table 1). Three hundred and four (24.7%) were found to be anaemic during a 12 month period. Sixty eight of these (22.4%) were identified as ''definite IDA'' (serum ferritin levels <20 μg/l, identified as the lower limit of normal range for the local laboratory). Of these 68, 44 (65%) had low MCV, but 56 (82%) had low MCH levels ($p = 0.016$, Fisher's exact test). In 36 patients with ''probable IDA'' (serum ferritin levels 20–100 μg/l), MCV was low in 14 (39%), but MCH was low in 26 (72%) ($p = 0.004$).

DISCUSSION

IDA is common and often difficult to identify accurately in patients with chronic inflammatory rheumatic diseases. Bone marrow aspiration remains the preferred test for its diagnosis, but has the disadvantage of being invasive. Thus, we are limited to using serological tests of iron stores, the best validated of which is serum ferritin, which is the most powerful test of iron deficiency.[4]

It has been proposed by Goddard *et al* that a serum ferritin concentration of >100 μg/l excludes IDA in the presence of concurrent inflammation, malignancy, or hepatic disease.[1] Further, though serum transferrin receptor assay can help to distinguish between the anaemia of chronic disease and iron deficiency, it is no better than serum ferritin.[5] However, there are no widely accepted guidelines for the diagnosis and management of IDA in our patient population, which represent a unique subset of patients.

Our study shows that a higher proportion of patients with both ''definite IDA'' and ''probable IDA'' had a low MCH compared with a low MCV. Low MCH correlated better with iron deficiency than low MCV.

Table 1 Patient characteristics

Age (years), mean (range)	60 (22–82)
Sex (%)	
Female	92
Male	8
Rheumatological diagnoses (%)	
Rheumatoid arthritis	76
Psoriatic arthritis	12
Seronegative spondyloarthropathy	8
SLE	2
Other	2

We suggest that in chronic inflammatory arthropathies, if the haemoglobin is low, then MCH is a better marker of iron deficiency than MCV. We therefore propose that MCH in conjunction with serum ferritin is a better predictor of IDA in patients with chronic inflammatory rheumatic diseases.

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Reactivation of a latent precore mutant hepatitis B virus related chronic hepatitis during infliximab treatment for severe spondyloarthropathy

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We report a case of hepatitis B virus (HBV) reactivation following the use of anti-tumour necrosis factor α (TNFα) antibodies that illustrates the need for careful viral monitoring and pre-emptive antiviral treatment in such patients.

CASE REPORT

A 35 year old white woman presented with a history of chronic hepatitis B without an increase in serum alanine aminotransferase (ALT) or detectable HBV DNA by a hybridisation technique since its diagnosis (in 1993); she was thus considered to be an asymptomatic HBV carrier. Her serological status was as follows: hepatitis B surface antigen positive, hepatitis B e antigen negative, hepatitis B e antibody positive, suggesting HBV precore mutant. Her rheumatological history began in September 2001 with oligoarthritis, inflammatory low back pain, limitation of motion, and anterior chest wall involvement. Symptoms improved incompletely with non-steroidal anti-inflammatory drugs. Biological inflammation (erythrocyte sedimentation rate 62 mm/1st h, C reactive protein 53 mg/l), positive HLA-B27 typing, and sacroiliitis on *x* ray examination completed the picture.

The patient did not respond to successive methylprednisolone boluses, sacroiliac injections of steroids, salazosulfapyridine, and methotrexate (15 mg/week) then associated with pamidronate infusions. No changes in transaminases or HBV DNA load were detected during this period.

Infliximab was started (5 mg/kg/infusion at weeks 0, 2, and 6) in August 2003, while she continued to receive methotrexate and non-steroidal anti-inflammatory drugs, with good response (over 50% improvement of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)) and return to a normal C reactive protein.

Follow up showed a progressive increase in serum transaminases, together with an increase in HBV DNA load assessed by quantitative real time polymerase chain reaction (TaqMan; fig 1), with persistent negativity of hepatitis B e antigen and positivity of hepatitis B e antibody. A 100 mg/day course of lamivudine treatment was promptly started in January 2004, while continuing infliximab every 8 weeks. This was followed by return to normal transaminase level, and undetectable HBV DNA load.

DISCUSSION

In this case of severe spondyloarthropathy, anti-TNFα treatment was, as expected, efficacious for treatment of the disease, but was followed by the first episode of HBV reactivation associated with hepatic cytolysis. In this case, infliximab was probably the culprit. Firstly, our patient was an asymptomatic HBV carrier, without any increase in serum ALT recorded over a long follow up period. Secondly, although she received methotrexate, which may favour HBV reactivation through its immunosuppressive properties[1] and induce subfulminant HBV reactivation after its withdrawal,[2 3] no change in HBV DNA load was seen during the 9 months of methotrexate monotherapy.

Although the mechanism involved in anti-TNF antibody induced HBV reactivation is not fully understood, it is well known that TNFα as well as interferon γ, is produced during the innate immune response in the liver[4] and has antiviral properties by inhibiting the replication of HBV DNA.[1] Moreover, inactivation of TNFα mediated apoptosis of cytotoxic lymphocytes by anti-TNFα antibodies may account for more severe liver disease.[5 6]

Our report is consistent with previously published cases of HBV reactivation after the use of infliximab.[1 7] In the first case, it occurred 16 months after starting infliximab for rheumatoid arthritis and was controlled with both lamivudine treatment and discontinuation of infliximab[1]; in two cases of Crohn's disease, reactivation of chronic hepatitis B occurred after withdrawal of infliximab.[7] Conversely, in another case of severe ankylosing spondylitis with chronic hepatitis B, a 1 year course of infliximab and methotrexate